# Clofazimine Pigmentation

To The Editor:

When Barry first started writing about the successful use of clofazimine he suggested that its extra-ordinary antituberculous effect in mice might be due to the fact that experimental tuberculosis is essentially an intracellular infection and suggested that the drug was phagocytosed into cells containing bacilli. It was this thought, combined with the fact that clofazimine is soluble in lipids that caused the initial work on B663 to be undertaken.

The paper by Sakurai and Skinsnes (IJL **45** [1977] 343-354) shows the presence of a brown pigmentation due to ceroid-like substance in macrophages in a series of three cases of lepromatous leprosy treated with clofazimine. This is indeed interesting but does not explain the blackish-brown pigmentation caused by lesions treated with oral clofazimine because such pigmentation also occurs in the undermined skin of *M. ulcerans* cases treated with clofazimine (Pettit: Br. J. Dermatol. **81** [1969] 794-795). I think it is reasonable to say that lipid-containing macrophages do not seem to be very common in the "buruli ulcer" pathology and so it would be logical to assume that the blackish-brown pigmentation cannot be entirely due to the findings reported by Sakurai and Skinsnes. I hope they will be able to report similar careful studies of hyperpigmented skins from such cases. It is also interesting to note that the successful use of clofazimine in *pyoderma gangrenosum* (Michaelsson *et al:* Arch. Dermatol. **112** [1976] 344-349) was not reported to be associated with any discoloration other than the usual redness. Perhaps studies on other diseases treated by this interesting drug should also be undertaken.

—John H. S. Pettit, M.R.C.P.

*Room 303, China Insurance Building*
*174 Jalan Tuanku Abdul Rahman*
*Kuala Lumpur, Malaysia*

Reply: *It is interesting, as Dr. Pettit notes, that a brown pigmentation also occurs in the undermined skin of* M. ulcerans *lesions treated with clofazimine and that the use of this drug in* pyoderma gangrenosum *is not reported to be associated with any discoloration other than the usually observed redness. We have no experience with this type of material. Dr. Pettit does not indicate whether or not the findings he refers to are based chiefly on routinely stained tissue sections or on extended histochemical studies comparable to those we utilized in studying the pigmentation process in lepromatous tissues.*

*Several observations and questions come to mind.*

1. *At what location in the skin does the pigment in* M. ulcerans *infection occur—epidermis, upper corium, lower corium, or subcutis? If it is in the epidermis or upper corium it might be melanin.*
2. *Ceroid may be deposited also extracellularly, as is often seen in atherosclerotic lesions. This pigment does not necessarily accumulate intracellularly.*
3. *A later stage brown pigmentation in leprous lesions may follow the destruction of bacillary waxy capsuls with oxidation of lipids. Our findings suggest that the color of the drug itself may not necessarily be the prime factor in the appearance of the lesion pigmentation occurring during its use. Metabolic changes related to the lipid materials from the bacillary capsuls and their oxidation processes, perhaps influenced by the drug, may be significant or even major factors in the development of this pigmentation. Dr. Pettit's observations may support this concept.*
4. *Macrophages ("foam cells") in lepromatous leprosy may have neutral fat in the lipid globules. Such neutral fat may contain carotenoid pigment and also soluble drug and these may play a role in pigment accumulation.*
5. *Melanin and/or hemosiderin may be deposited in skin around ulcerations such as those of* M. ulcerans *infection and need to be differentiated from other pigments.*

*It would appear that careful histochemical studies of diseases other than leprosy where clofazimine is used are needed to help determine whether or not the pathogenesis of pigment formation in these instances truly differs from the findings we reported. Though we had a limited series of lesions for our study the findings were consistent.*

—Isamu Sakurai, M.D., Sc.D.

*Department of Pathology*
*Nihon University School of Medicine*
*Itabashi-ku, Tokyo 173, Japan*